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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,695	03/17/2004	Laszlo Prokai	T2315-907327US02	1881

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EXAMINER	
PATEL, SUDHAKER B	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/801,695	PROKAI, LASZLO	
	Examiner	Art Unit	
	Sudhaker B. Patel, D.Sc.Tech.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 March 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. It is noted that this application appears to claim subject matter disclosed in prior Application No. 10109000, filed 3/29/02. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. Also, the current status of all nonprovisional parent applications referenced should be included.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims1-6 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-13 of copending Application No. 1010900, filed 3/29/02.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The ref.'900 claim 1 recites the compounds of Formula (I) as claimed herein. The instant claims differ from the ref.'900 by reciting a broader genus than the ref.'900, but they read onto the ref.'900 claims, which would extend, the monopoly, if ref.'900 matures to a patent.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling treating for a specific single disease or condition e.g. nicotine addiction, does not reasonably provide enablement for attenuating effects of opiate- addiction, -dependence, -tolerance, -abstinence syndrome, and obesity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The claims are not only reciting treating of a single disease, but

attenuating opiate related disorders, and eating disorder, namely obesity, and diseases yet not discovered.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:*(1).* The nature of invention;*(2).* the state of prior art ;*(3).* the predictability or lack thereof in the art;*(4).* the amount of direction or guidance present;*(5).* the presence or absence of working examples;*(6).* the breadth of the claims, and *(7).* the quantity of experimentation needed.

1) The nature of the invention: The method of use claims are drawn in part to treating of diseases related to opiate receptors. The diseases include in addiction to nicotine addiction, ameliorating and attenuating effects of opiate- addiction, -dependence, -tolerance, -abstinence syndrome, and obesity, and many other diseases related to CNS and as recited herein.

2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to ameliorating and attenuating effects of opiate- addiction, -dependence, -tolerance, -abstinence syndrome, and obesity nor is there any compound that can be used to treat all diseases related to CNS receptors' activity in general by a single compound. For example, the notion that a compound could be effective against chemical substance abuse or withdrawal caused by the cessation of intake of chemical substances in general is absolutely contrary to our current understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for "chemical substance abuse or withdrawal caused by the cessation of intake of chemical substances" generally. That is because "chemical substance/alcohol/opiate abuse or withdrawal caused by the cessation of intake of chemical substances" is not a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc. all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine reuptake transmitter. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find a pharmaceutical to treat chemical addictions generally have thus failed. Alzheimer's disease, which is CNS, related disease is treatable, albeit not successfully, using acetylcholine esterase inhibitors and Parkinson's disease using dopamine receptors. A disease in the central or peripheral system is not a single disease but embraces diseases that are not related or even "opposites".

3) The predictability or lack thereof in the art: It is presumed in the treatment of the diseases claimed herein there is a way of identifying any and all of the diseases which are responsive to the activity of opiate receptors. There is no evidence of record, which

would enable the skilled artisan in the identification of the diseases treatable with the disorders claimed herein.
4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present for treatment of the disorders recited.
6) The breadth of the claims: The claims are drawn to disorders that are not related and whose treatment is unknown.
7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Following references are cited to show the state of art related to a few of the diseases recited herein:

- ***Characterization of neurobiological theories of addiction:***

Lingford-Huges AR et al(PubMed Abstract 12697627, also cited as Br. Med. Bull., 65. 209-22(2003)) states that:" The neurochemistry of addiction, particularly involving dopamine, serotonine, opiate and GABA, has been studied with PET and SPECT and similarities between all drugs of abuse have been found such as reduced popaminergic markers. The evidence derived from these advances in neuroimaging **is likely** to herald the emergence of new biological treatments in this important field".

- ***Interaction between NPFF and opioids in the VTA area in the behavioral response to novelty:***

Cador M. Marco et al(PubMed Abstract 11958872, also cited as Neuroscience, 110/2,309-18(2002)) state that:" Taken together, these results suggest that **NPFF neurons may participate** at the level of the VTA to a homeostatic regulating process counteracting opioid effects induced by a mild stress such as novelty".

- ***Role of NOS inhibition and NPFF;***

Malin D.H> et al(PubMed abstract 8804070, also cited as Peptides, 17/4,615-8(1996)). State that:" The anti-NPFF activity of 15 mg/Kg L-NNA was blocked by 750 mg/kg **L-arginine, but not by the same amount of D-arginine**, indicating that L-NNA attenuates NPFF activity through a stereospecific inhibition of NOS".

- ***Hypothesis related to Opioid modulation of taste hedonics with the ventral striatum:***

Kelley et al(PubMed Abstract 12117573, also cited as Physiol Behav., 76/3,389-95(2002)) state that:" We hypothesize that opoid-mediated mechanisms within ventral striatal medium spiny neurons mediate the affective or hedonic response to food('liking' or food 'pleasure'). Further refinement of this hypothesis is that activation of ventral striatal opioid..specifically encoded positive affect induced by tasty and or calorically sense food (such as sugar and fat), and promotes behaviors associated with this enhanced palatability".

- ***Studies related to the function of gene encoding the human NPFF:***

Nystedt et al(PubMed Abstract 12354280, also cited as J. Neurochem.,82/6,1330-42(2002)) state that:" We postulate that control of human NPFF gene expression is the result of both positive and negative regulatory elements and the use of multiple transcription initiation sites".

Specification on pages 11-13 recite various methods of assays and tests carried out by the applicants for the instant compounds.

Specification summarizes the results as:" On the basis of physicochemical properties, structural features, and Immobilized artificial membrane(IAM) chromatography, test compound 5 afforded an increase compared to compound 3 in its predicted CNS bioavailability".

These results are not sufficient to support the methods of use claims claiming treating as well as for ameliorating and attenuating effects of opiate- addiction, -dependence, -tolerance,-abstinence syndrome, and obesity ,and many other disease related to CNS. These results will help as preliminary guideline for screening the compounds only.

Statements of utility, which relate to or imply to treatment of a disease are subject to closer scrutiny. Ex parte Moore et al.(POBA 1960) 128 USPQ 8. Claims 3-7 do not meet the Utility Guidelines. The claims do not qualify as one utility statement, and are not believable on their face. Claims will require too much experimentation to determine what patient dosage relationship would produce what results. It is not believable on its face that any one compound would have all of those utilities. In re Hozumi, 226 USPQ 353.

The quantity of experimentation need would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skilled in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims involving use of compounds, their compositions.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-2 are rejected under 35 U.S.C. 102(a) as being anticipated by Prokai et al(J. Med. Chem.,44,1623-26(2001)).

The reference compound read on instant claims with following meanings in Formula (I):

Z = not involving P = SO2-NH-CH2CO- ;

Dashed lines and R' absent = compounds are not forming ring with-N(H)-X-N(H)-;

R3 = Non-heterocycle ;

Y = -CH = CH- i.e Naphthalene ring ;

R6 =5-(CH2)n-NR12R13 = 5-N(Alkyl)2 i.e. n =zero;

R5,R1 and R2 =H;

W = -CnH2n-m-NH- = -(CH2)3-NH-

X = -CH(R4)-CO-, & R4 =-(CH2)-OH, n = 1.

Compound having CAS RN # 342045-44-7 read on to instant claims 1-2.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tan et al(Peptides, 20,1211-17(1999)as applied to claims 1-13 above, and further in view of over Prokai et al(J.Med.Chem. 44,1623-1626(2001), also cited as Chemical Abstract 135:163).

8. The ref. teaches modulation of naxolone-precipitated morphine withdrawal syndromes in rats by neuropeptide FF analogues. See compounds and structures in page 1213. The ref. compound (3) differs from the instant compounds by having a pyrrolidine ring i.e. a core:" 5-Dimethyl-N- Substituted naphthalene-SO2-**N pyrrolidine**-CO-NH-CH(CH2-CH2-CO-NH2) -CO-NH-CH(CH2-CH2-CH2-NH-C(=NH) Nh2) -CO-NH2".

9. The other ref. Prokai teaches making of a lead optimization compound having a Chemical Abstract CAS RN # 142045-44-7.

10. The ref. Prokai differs from the instant compounds by either having a –CH2- group attached to –OH groups or by having -NH- linked to –(CH2)3- group instead of –(CH2)4- without –NH- bridge.

Thus, it would have been obvious to one having ordinary skill in the art at the time of invention to prepare instant compounds by modifying or replacing as:

(I). Replacing –N pyrrolidine-CO bridge by open structutre: "—NH-CO- ".

(II) Reducing the chain length from-CH2-CH2-CO-NH2 to "—CO-NH2".as taught by Prokai.

(III).Increasing the chain length from –CH2-CH2-CH2-NH to –CH2-CH2-CH2-CH2-.

(IV). Either retaining the –NH- group or deleting the –NH-group in (III). above,

and try out the use/utility as a pharmaceutical by using the conventional chemistry knowledge. The motivation stems from the expectation of making compounds having equal or better pharmaceutical agent.

Analogous alkaline bridge variations would be structurally obvious. See, In re Dillon, 919 F. 2d at 1904. See also Deuel, 51 F. 3d at 1558, 34 U.S.P.Q. 2d at 1214 ("Structural relationships may provide the requisite motivation or suggestion to modify one compound to obtain another compound(s)"). For example, one compound may suggest its homologue/isomer, because homology/isomer often have similar properties, and therefore, chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties, or merely to satisfy their production goals.

11. Claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F. 2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP 2141.02.

12. It has been held that a prior art disclosed compounds is sufficient to render a prima facie case of obviousness as species falling within a genus. See In re SUSI, 440 F 2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by Federal Circuit in Merck & co. V. Biocraft Laboratories, 847 F 2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir.1989).See In re Dillon 16 USPQ 2nd. 1897, 1923 regarding a prima facie case of obviousness of structurally similar compounds disclosed by prior art" regardless lo the properties disclosed in the inventor's application.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is (571) 272-0671.

The examiner can normally be reached on 6:30 to 5:00 pm (Monday-Thursday). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on (571) 272 0674 or Sr. Examiner Mr. Richard Raymond at (571) 272 0673 or Mr. James O. Wilson at (571) 272-0661.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sudhaker B. Patel, D.Sc. Tech.
June 21, 2004

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